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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,679	08/16/2005	Richard Bell	PG4798USW	2845

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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,679	BELL ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The 102 (b) rejection over Hcaplus 117:131082 has been withdrawn in light of applicant's comments filed 4/6/06. The 103 (a) over Grimova is withdrawn because the compound is actually a 102 (b) compound. The 112, second paragraph rejection of claim 17 is withdrawn in light of applicant's amendment filed 4/6/06. Claims 20-21 are withdrawn from consideration. The Restriction Requirement and Election of Species Requirement is maintained and made FINAL.

(old rejections)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 10, 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friebe et. al. (See Reference A).

Friebe et. al. teaches the compound as shown in Formula I, where A is alkylene with 1 to 2 carbon atoms, B is an oxygen atom, mi is 1, X is a valency bond, Y is a valency bond, Z is halogen, C1-to C6 alkyl, R is COOH. At the abstract, see the compound of formula I and the radicals defined. The difference between the prior art compound and the instantly claimed compounds is the teaching of a genus that overlaps in subject matter with the instant genus. The patentee teaches a very limited

number of selections for the variables of this genus that are small enough in number to be combined to form the instant genus. Since the patentee teaches a small group of compounds within a genus that overlaps in subject matter with the instant genus, it would have been obvious for one of ordinary skill in the art to easily envision and test the compounds that overlap with the prior art genus of compounds. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

(new rejections)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

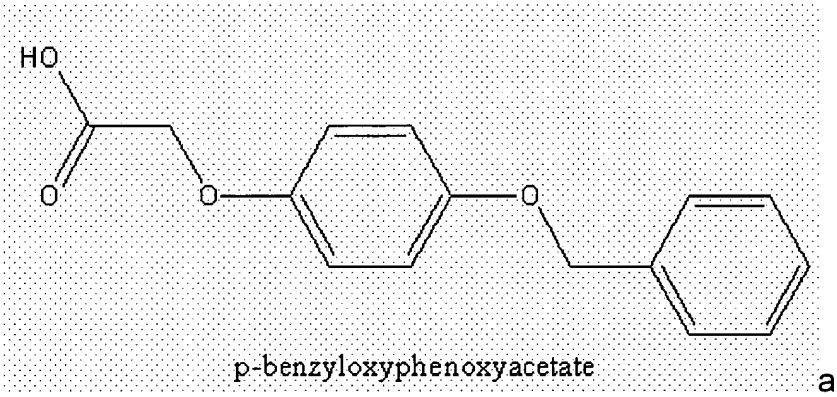
Claims 1-5, 10, 13, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Friebe et. al. (US Patent 5399575). At column 8, lines 40-44, see for example, compound 4-[2-(4-pyridinyl)ethyl]-phenoxyacetic acid. The Friebe compound anticipates these claims because the moiety corresponding to the instant X moiety is O, the atoms corresponding to R1 and R2 are H, the moieties corresponding to R3 and R4 are H, the moiety corresponding to X1 is CH2, the moieties corresponding to R5 and R6 are H, and R7 is a pyridinyl ring.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9-10, 13, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et. al. (Journal of Medicinal chemistry, 1972, Vol. 15, No. 9.

Baker et. al. discloses the instant compound



p-benzyloxyphenoxyacetate at page 942, column 1, line 28, see compound 54. Compound 54 anticipates the instant compounds, because of the presence of an acetate group bonded to a moiety corresponding to the instant X group, the moiety corresponding to the instant X group is 0, R^1 and R^2 are hydrogen, R^3 and R^4 are hydrogen, X^1 is O, R^5 and R^6 are hydrogen and R^7 is phenyl.

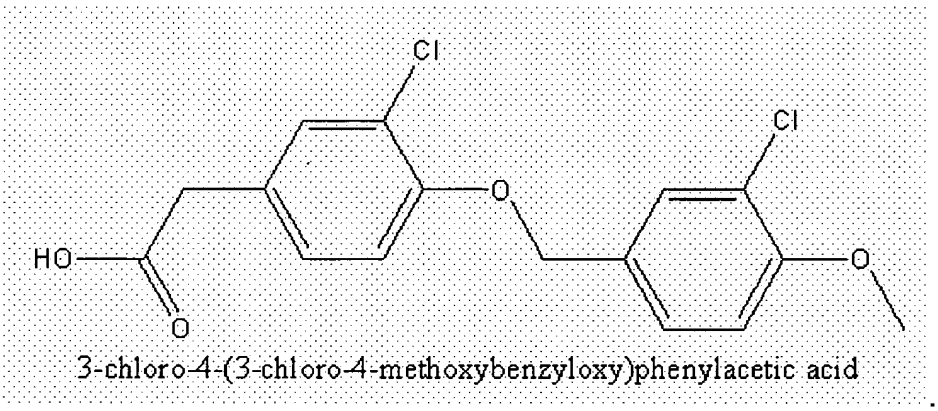
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 9, 10, and 17are rejected under 35 U.S.C. 102(b) as being anticipated by Grimova et. al.

Grimova et. al. discloses the instant compound,



3-chloro-4-(3-chloro-4-methoxybenzyloxy)phenylacetic acid

. At column 3, lines 50-55, see example 1. The Grimova et. Al. compound anticipates the instant claims, because the radicals corresponding to R1 and R2 are H, the radical corresponding to X is (CH2)n wherein n is 0, the radicals corresponding to R3 is chlorine which is a halogen atom, the radical corresponding to R4 is hydrogen, the radical corresponding to X1 is O, the radicals corresponding the R5 and R6 are H, the moiety corresponding to the R7 moiety is pyridinyl substituted by halogen which is chlorine and methoxy.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I wherein R7 is phenyl

optionally substituted as claimed in these claims, or pyridinyl optionally substituted as claimed, does not reasonably provide enablement for the compounds of formula I wherein R7 is a 6-membered heteroaryl ring containing 2 to 3 nitrogen atoms optionally substituted as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection are summarized below:

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

a) Determining if any particular claimed compounds of formula I wherein R7 is a 6-membered heteroaryl ring containing 2 to 3 nitrogen atoms, optionally substituted as claimed would be active would require synthesis of the substrate and subjecting it to testing with Applicants' in vitro binding and transfection assays. Considering the large number of compounds to be made, this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found in

lines 10-28 of page 77, and on pages 78-142, which merely states Applicants' intent to make and use such compounds. c) In the instant case none of the working examples are compounds where R7 is a 6-membered heteroaryl ring containing 2 to 3 nitrogen atoms. There is much unpredictability since one could not predict how compounds wherein R7 is a 6-membered heteroaryl ring containing 2 to 3 nitrogen atoms will act on the PPARδ properties of these compounds significantly differ from the chemical an biological activity of compounds wherein R7 is phenyl or pyridine. For example, diazines are weak bases in comparison to pyridine which is a stronger base than the 6 membered diazines. See page 68 of Palmer.

d) The nature of the invention is activation of PPARδ αnd treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the PPARδ receptor, the binding activity of small ligands to that receptor, and the ability of those compounds to activate PPARδ. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) The state of the art of detailed knowledge of the PPARδ receptor is lacking. The six-membered benzene rings of Applicants' working example compounds, 1-4, 6-7, 9-114, 38, 39, 136-141 is non-basic. The pyrimidine ring, pyridazine, the pyrazine ring, and triazine 6-membered rings of the rejected compounds are weakly basic. The 6 membered heteroaryl ring containing 2 to 3 N of the rejected compounds are hydrogen bond acceptors. The benzene ring of Applicants' working examples is not. The pyrazine ring of the rejected compounds are π-electron deficient. The benzene ring of Applicants' working examples is not. The six-membered pyridine of Applicants' working example compounds, 5,8, 15, 16-37, 40-135, 142-144 are more basic in comparison to the compounds wherein R7 is a 6 membered diazine which is weakly-basic. The properties of triazines differs significantly from that of diazines and from phenyl. For example, pyrimidine has a melting point of 22.5, whereas pyrazine has a melting point of 54 degrees and pyradazine has a melting point of –6.4 degrees. See table 3.1 page 66 of Palmer. Pyrimidine is not obvious over any 6 membered triazine or over phenyl for example. There is no reasonable basis for the assumption that the myriad of compounds embraced by the present formula (I) will all share the same biological properties. For example, the rings include pyrimidine, pyradizine, pyrazine which are weak bases as compared to pyridine in the applicants working examples which

is a stronger base. The diverse claimed 6 membered heteroaryl rings containing 2 to 3 nitrogen atoms are chemically non-equivalent to phenyl and pyridine and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

Compounds made and tested represent the scope of claims 1-14, 17 wherein R7 equals phenyl optionally substituted as claimed or pyridine optionally substituted as claimed, not claim 15, or those portions of claims 1-14 and 17 wherein R7 can equal a 6-membered heterocyclic ring containing 2 to 3 nitrogen atoms, wherein the ring can be optionally substituted as claimed.

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of thousands of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific

compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 15 is rejected because it is not written in proper format; the phrase "selected from" in line 1, page 4, should be amended to "selected from the group consisting of".

Response to Applicant's Remarks

Traversal of the Lack of Unity Holding

Applicants traverse the lack of unity holding, stating that ζMPEP 1850 (C) states that unity of invention shall be construed as permitting the inclusion of product claims with method of use claims in the same application and therefore, withdrawal of the restriction is proper. However, this is only true if the instant compounds are free of the prior art, making a contribution over the prior art(novel and unobvious), that unity of invention is accepted between the product claims and the method claims. Support comes from PCT Rule 13.2 and 37 CFR 1.475(b)(2), (c) and (d). Unity of invention is lacking between a product and method of making or using that product when there is prior art on the product as is the case here as indicated in the last office action mailed 1/10/06. However, as is the situation in this case, if there is prior art on the instant compounds, then the technical feature is not special and the USPTO is not required to group a product with its method of use. The reasoning is due to the fact that the instant compounds do not make a contribution over the prior art and do not link the product and method claims into a single general inventive concept.

Traversal of the election of Species Requirement

The applicants also traverse the election of species requirement, alleging that the examiner's finding that the species lack the same or corresponding "special technical feature" that defines a contribution over the prior art. The applicants then state that Markush practice shall be considered to be met when the chemical alternatives are of a similar nature which can be demonstrated when all alternatives have a common property or activity and a common structure is present, i.e. a significant structural element is shared by all of the alternatives. Applicants allege that all of the compounds

have a common structural element. However, this is not so since for example, X and X1 can be O or CH2 and an oxygen atom has chemical properties that are significantly different from the chemical properties of an methylene group. Additionally, R7 can be a phenyl ring or any 6 membered heteroaryl ring containing from 1 o 3 nitrogens. A phenyl ring contains significantly different chemical properties from a pyridine ring or a pyrimidine ring for example, and a pyrimidine ring contains significantly different chemical properties from a pyridine ring and these rings are not obvious over one another. Applicants also allege that all of the alternatives have a common property or activity of activating PPARδ. However, as stated on page 3 of the last outstanding office action mailed 1/10/06, the compound Butanoic acid, 4-p4-[2-(3-methyl-4-pyridinyl)ethyl]phenoxy is used as an allergy inhibitor (See US 5399575), whereas the compound GC-1, is a thyroid hormone receptor inhibitor. See Chiellini et. al. The applicant has not traversed the findings that these 2 particular alternatives have different activities and has not stated how all of the alternatives of the instant genus of compounds all have a common core.

Friebe 103(a) rejection

Freibe et. Al. 103 (a) rejection. The applicant traverses this103 (a) rejection alleging that the overlap of the Freibe compounds with the instant compounds is so small that one skilled in the art would be left without the necessary teachings and motivations to arrive at the instant invention. The applicant then points on page 23 of the response to the Friebe compound where the radical Z is halogen or C1-6 alkyl, and bonding of the radical is in the 2-, 3- or 4- position of the pyridine; and compares this compound with

the instant invention wherein R7 is phenyl or a 6-membered heteroaryl group containing 1, 2, or 3 – nitrogen atoms wherein the phenyl or heteroaryl group is substituted by 1, 2, or 3 moieties selected from the group consisting of halogen, C1-6 alkoxy, C1-6 alkyl, CF3, hydroxyl, or phenyl (which may be optionally substituted by one or more C1-3 alkyl, -OC1-3 alkyl, CN, acetyl, hydroxyl, halogen or CF3), alleging that the modifications required to go from the Friebe compounds to arrive at the instant compounds are substantial. However, this is not so. The instant compounds anticipate this particular Friebe compound mentioned because when R7 in the instant compound is a 6 membered heteroaryl ring containing 1 nitrogen substituted with halogen or C1-6 alkyl, this moiety reads on the pyridinyl moiety in the Friebe compound, where Z is C1-6 alkyl or halogen bonding at the 2, 3, or 4 position of the pyridine rings and n is 0, since pyridinyl ring is a heteroaryl ring with 1 N. The remaining radicals in the Friebe compound are also anticipated by the instant compound, since A in the Freibe compound can be C1-3 alkylene, and the corresponding X1 moiety bonded to the CH2(R6in the instant compound can be CH2). The applicant alleges that the required modifications to arrive at the compounds here are substantial, however, this is not at all the case, since these compounds anticipate the instant compounds.

The references that have been crossed out on the IDS filed 12/17/04 will not be considered until the references have been provided to the examiner. Binta Robinson

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Thomas Mckenzie can be reached on 571-272-0670.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
June 9, 2006

Thomas C. McKenzie
SPE
AU 1625